

### REMARKS

By the above amendment, claim 8 has been amended in a manner which overcome the rejection under 35 USC 112, second paragraph with the other claims being amended to clarify features of the present invention and which features patentably distinguish over the cited art as will be discussed below. Additionally, new claims 13-20 have been added wherein claims 13-15 are independent claims more particularly reciting features of the DNA analysis system as recited in claims 1-12 and claim 16 is an independent claim directed to a DNA analysis method corresponding to the features of the system with claims 17-20 being dependent claims directed to the method of claim 16.

Turning to the rejection of claim 8 under 35 USC 112, second paragraph as being indefinite, by the present amendment, claim 8 has been amended to delete the reference to the "system administrator" such that this rejection should now be overcome.

As to the rejection of claims 1-6 under 35 USC 102(b) as being anticipated by Koster (U.S. Patent No. 5,605,798); the rejection of claims 1-10 under 35 USC 103(a) over Koster (U.S. Patent No. 5,605,798) in view of Haff, et al. (U.S. Patent No. 5,885,775); and the rejection of claims 1-12 under 35 USC 103(a) over Koster (U.S. Patent No. 5,605,798) in view of Haff, et al. (U.S. Patent No. 5,885,775) further in view of Harris, et al. (U.S. Patent No. 4,353,242) such rejections are traversed insofar as they are applicable to the present claims and reconsideration and withdrawal of the rejections are respectfully requested.

At the outset, as to the requirement to support a rejection under 35 USC 102, reference is made to the decision of In re Robertson, 49 USPQ 2d 1949 (Fed. Cir. 1999), wherein the court pointed out that anticipation under 35 U.S.C. §102 requires that each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. As noted by the court, if the prior art reference does not expressly set forth a particular element of the claim, that

reference still may anticipate if the element is "inherent" in its disclosure. To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." Moreover, the court pointed out that inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

With regard to the requirements to support a rejection under 35 U.S.C. 103, reference is made to the decision of In re Fine, 5 USPQ 2d 1596 (Fed. Cir. 1988), wherein the court pointed out that the PTO has the burden under §103 to establish a prima facie case of obviousness and can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. As noted by the court, whether a particular combination might be "obvious to try" is not a legitimate test of patentability and obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. As further noted by the court, one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.

Furthermore, such requirements have been clarified in the recent decision of In re Lee, 61 USPQ 2d 1430 (Fed. Cir. 2002) wherein the court in reversing an obviousness rejection indicated that deficiencies of the cited references cannot be remedied with conclusions about what is "basic knowledge" or "common knowledge". The court pointed out:

The Examiner's conclusory statements that "the demonstration mode is just a programmable feature which can be used in many different device[s] for providing automatic introduction by adding the proper programming software" and that "another motivation would be that the automatic demonstration mode is user

friendly and it functions as a tutorial" do not adequately address the issue of motivation to combine. This factual question of motivation is immaterial to patentability, and could not be resolved on subjected belief and unknown authority. It is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to "[use] that which the inventor taught against its teacher."... Thus, the Board must not only assure that the requisite findings are made, based on evidence of record, but must also explain the reasoning by which the findings are deemed to support the agency's conclusion. (emphasis added)

As described at page 47, lines 13-21 of the specification of this application, the present invention provides a DNA analysis system and method wherein plural types or kinds of multiply-charged ions with five or more charges are generated, detected and checked with predicted results. Thus, the present invention enables a stable measurement to be achieved even though the concentration of the sample is substantially smaller than the appropriate concentration thereof with a high-throughput measurement being obtained over a long period of time. Applicants note that Figures 1, 10 and 14, for example illustrate the system of the present invention and as recited in independent claim 1, there is provided a DNA analysis system for analyzing DNA polymorphism which includes ionization used for generating plural kinds of multiply-charged ions of a test DNA fragment, where each of the multiply-charged ions has five or more charges, a mass spectrometer for performing mass spectrometry on the multiply-charged ions formed by the ionization means so as to measure a mass spectrum of the test DNA fragment, and analyzing-result prediction means that predicts possible mass spectrum patterns in each of two cases, where one of the two cases is that the test DNA fragment is polymorphic and an other of the two cases is that the test DNA fragment is not polymorphic, based on both an information including a number of each of four different nucleic acid bases that constitute the test DNA fragment and an information about a polymorphism point, and a comparator processor for comparing a plurality of the predicted mass

spectrum patterns with the measured mass spectrum to determine a nucleic acid base on the polymorphism point as described for example at page 6, line 19 to page 7, line 18, for example. In this regard, it is noted that claim 1, by the present amendment, has been amended to clarify the aforementioned features including utilizing information of a number of each of four different nucleic acid bases that constitute the test DNA fragment.

In setting forth the rejection of claims 1 and 6 based upon Koster under 35 USC 102, the Examiner apparently contends that Koster discloses ionization means for generating plural kinds of multiply-charged ions of a test DNA fragment, where each of them has five or more charges (Example 2, Figures 11B and C, Column 2, lines 46-61, and Column 11, lines 2-10). Irrespective of this position by the Examiner, in that Koster describes the possible use of an ionizer, and irrespective of the Examiner's position that mass spectrometry is performed on multiply-charged ions, Applicants submit that there is no disclosure in Koster in the sense of 35 USC 102 of the generation of plural kind of multiply-charged ions of a test DNA fragment, where each of the multiply-charged ions has five or more charges. Furthermore, irrespective of the Examiner's position concerning analyzing high-result prediction means as being disclosed in Figure 1C of Koster and that comparative processing means are disclosed in other figures and portions of the specification of Koster, Applicants submit that Koster does not disclose in the sense of 35 USC 102, analyzing-result prediction means for predicting possible mass spectrum patterns as recited in claim 1 nor comparative processing means for comparing a plurality of predicted mass spectrums with the measured mass spectrum to determine a nucleic acid base on the polymorphism point as recited in claim 1 nor the other recited features of the dependent claims of this application in the sense of 35 USC 102. as noted in In re Robertson, supra, inherency can not be shown by mere possibilities. Applicants submit that the claimed features as set forth in claim 1 and the dependent claims of this application are not disclosed or taught by Koster in the

sense of 35 USC 102 such that claim 1 and the dependent claims patentably distinguish thereover and should be considered allowable at this time.

With respect to the features of the dependent claims, irrespective of the position by the Examiner, Applicants note that the dependent claims recite additional features of the present invention and in particular claim 4, has been amended to define a treatment to obtain S(i) for the measured mass spectrum I(i) at an ordinal number "i" as described at page 46, line 10 at seq of the specification. Other dependent claims recite additional features not disclosed or taught by Koster and Applicants submit that independent claim 1 and the dependent claims patentably distinguish thereover and should be considered allowable at this time in the sense of 35 USC 102 and 35 USC 103.

With regard to the combination of Koster and Haff, et al., the Examiner recognizes that Koster does not teach the DNA analysis system comprising display means for displaying the occurrence of an emergency in the manner defined. Irrespective of this recognition of the deficiency of Koster, Applicants submit that Koster does not disclose or teach the claimed features of claim 1 and the dependent claims. The Examiner contends that Haff, et al. teach the display means operating in the manner defined and that it would have been obvious to combine the same. Applicants submit that this position by the Examiner represents a hindsight reconstruction of the present invention utilizing the principal of "obvious to try" which is not the standard of 35 USC 103. See In re Fine, supra. Applicants submit that irrespective of the Examiner's position concerning the disclosure of Haff, et al., Haff, et al. does not overcome the deficiencies of Koster as pointed out above. More particularly, Koster discloses that mutated types can be distinguished from wild types by mass spectrometry without providing the claimed features as discussed above, and Haff, et al. merely discloses a method for bringing the concentration level of an extended primer above the threshold sensitivity of the mass spectrometer. Applicants submit that such combination fails to provide the claimed

features as recited in claim 1 and the dependent claims in the sense of 35 USC 103 such that all claims should be considered allowable thereover.

Applicants note that in addition to the deficiencies of Koster and Haff, et al. with respect to the features of claim 1, and at least dependent claim 4, as pointed out above, this combination fails to disclose or teach display means for displaying occurrence of an emergency, a maximum ion intensity detected by the mass spectrometry means is smaller than a predetermined threshold as recited in claim 7, communication means for generating information about the occurrence of the emergency as recited in claim 8, introducing of the standard sample to the ionization means by the sampling means when a maximum ion intensity of a mass spectrum detected by the mass spectrometry means is smaller than a predetermined threshold, as recited in claim 9 or re-supply of the sample to the ionization means by the sampling means at a particular time as recited in claim 10. It is apparent that the combination of Koster and Haff, et al. fail to provide these claimed features in the sense of 35 USC 103 and Applicants submit that such features can not be considered well known features or the like which can be combined to provide the claimed invention. See In re Lee, supra. Thus, Applicants submit that claims 1-10 patentably distinguish over this proposed combination of references in the sense of 35 USC 103 and such claims should be considered allowable at this time.

As to the addition of Harris, et al. to the combination of Koster and Haff, et al., the Examiner contends that Harris, et al. teach the analysis system, where the occurrence of the emergency information is transmitted to sampling means of another measurement system. Applicants submit that irrespective of the Examiner's position, Harris, et al. merely discloses a typical computer use and a GC-MS provided with a computer. Applicants submit that Harris, et al. does not overcome the deficiencies of Koster and Haff, et al. as pointed out above, and the proposed combination represents a hindsight reconstruction attempt of the present invention without regard of the teachings of the individual references and is not proper in the

sense of 35 USC 103. Thus, Applicants submit that claims 1-12 patentably distinguish over this proposed combination of references in the sense of 35 USC 103 and should be considered allowable thereover.

With respect to the newly added claims, Applicants submit that each of newly added claims 13-15 in addition to reciting features similar to that recited in claim 1 which patentably distinguishes over the cited art for the reasons given above, also recite the obtaining of S(i) in the manner defined corresponding to the recited features of claim 4 which features are not disclosed or taught in the cited art. Thus, Applicants submit that claims 13-15 should also be considered allowable at this time.

With respect to independent claim 16 and the dependent claims, Applicants submit that claim 16 is a method claim reciting features corresponding to the features recited in claim 1 and patentably distinguishes over the cited art for the reasons indicated above. Claims 17-20 recite features corresponding to that of the claims which depend from claim 1 which features are also not disclosed or taught in the cited art. Thus, Applicants submit that these claims should also be considered allowable at this time.

In view of the above amendments and remarks, Applicants submit that all claims present in this application, should now be in condition for allowance, and issuance of an action of a favorable nature is courteously solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current Amendment. This marked-up version is on the attached pages, the first page of which is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE".

To the extent necessary, Applicants petition for an extension of time under 37 CFR § 1.136. Please charge any shortage in fees due in connection with the filing

of this paper, including extension of time fees, to the Deposit Account No. 01-2135  
(Case No. 1021.40593X00) and please credit any excess fees to such Deposit  
Account.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Please amend claims 1-4 and 8-12 as follows:

1. (amended) A DNA analysis system for analyzing DNA polymorphism, comprising:

ionization means for generating plural kinds of multiply-charged ions of a test DNA fragment, where each of them the multiply-charged ions has five or more charges;

mass spectrometric means for performing a mass spectrometry on the multiply-charged ion ~~ions~~ formed by the ionization means so as to measure a mass spectrum of the test DNA fragment;

analyzing-result prediction means that predicts a possible mass spectrum ~~pattern from the mass spectrometric means patterns~~ in each of two cases, where one of the two cases is that the test DNA fragment is polymorphic and ~~the an~~ other of the two cases is that the test DNA fragment is not polymorphic, based on both an information ~~about including a number of each of four different nucleic acid bases that constitute~~ the test DNA fragment and an information about a polymorphism point; and

comparative processing means for comparing a plurality of the predicted mass spectrum patterns ~~predicted by the analyzing-result prediction means~~ with the ~~analyzing results of the test DNA fragment analyzed by the mass spectrometric means~~ measured mass spectrum to determine a nucleic acid base on the polymorphism point.

2. (amended) The DNA analysis system according to claim 1, wherein the analyzing-result prediction means predicts a mass-to-charge ratio ( $m/z$ ;  $m$  is an ion mass,  $z$  is ~~the a~~ number of electric charges) of each of the plural kinds of ~~multi-charged~~ multiply-charged ions in each of the two cases, ~~where one is that the test DNA fragment is polymorphic and the other is that the test DNA fragment is not~~

polymorphic and the comparative processing means compares the predicted mass-to-charge ratio ( $m/z$ ) of the predicted mass spectrum patterns with a mass-to-charge ratio ( $m/z$ ) of the measured mass spectrum.

3. (amended) The DNA analysis system according to claim 1, wherein the analyzing-result prediction means predicts a mass-to-charge ratio ( $m/z$ ;  $m$  is an ion mass,  $z$  is the number of electric charges) of each of the plural kinds of multi-charged multiply-charged ions and a distribution of ion intensities relative ion intensity corresponding to the mass-to-charge ratio ( $m/z$ ) in each of the two cases, where one is that the test DNA fragment is polymorphic and the other is that the test DNA fragment is not polymorphic and the comparative processing means compares the predicted mass-to-charge ratio ( $m/z$ ) of the predicted mass spectrum patterns with a mass-to-charge ratio ( $m/z$ ) of the measured mass spectrum and compares the predicted relative ion intensities of the predicted mass spectrum patterns with relative ion intensities of the measured mass spectrum.

4. (amended) The DNA analysis system according to claim 1, further comprising:

sampling means for supplying a sample including the test DNA fragments fragment to the ionization means intermittently at fixed intervals a predetermined time period; and

detecting-output analysis means for subtracting a mass spectrum obtained as an analyzing result with respect to a sample previously measured and modified by weight from a mass spectrum obtained as a detecting output of the mass spectrometric means, wherein

the mass spectrum processed by the detecting output analysis means is provided as an analyzing result with respect to the test DNA fragment in the sample performing the following treatment to obtain  $S(i)$  for the measured mass spectrum

(I(i)) at an ordinal number "i".

$$S(i) = I(i) - \sum_{n=1}^m w(n)I(i-n)$$

wherein m represents a predetermined natural number and w(n) represents a factor that represents a level of influence of the sample measured at n-th before the measurement of the sample which is measured i-th, and

wherein the S(i) is compared with each of the predicted mass spectrum patterns.

8. (amended) The DNA analysis system according to claim 7, further comprising:

communication means for ~~sending~~generating information about the occurrence of the emergency ~~to a system administrator.~~

9. (amended) The DNA analysis system according to claim 4, wherein the sampling means introduces a standard sample into the ionization means when a maximum ion intensity of the measured mass spectrum ~~detected by the~~ mass spectrometric means is smaller than a predetermined threshold.

10. (amended) The DNA analysis system according to claim 9, wherein when a maximum ion intensity of a mass spectrum of the standard sample detected by the mass spectrometric means is equal to or higher than the predetermined threshold, the sample where the maximum ion intensity of the mass spectrum is detected as one smaller than the predetermined threshold is re-supplied to the ionization means by the sampling means.

11. (amended) The DNA analysis system according to claim 9, further comprising:

a plurality of measurement systems, where each of the measurement

systems comprises the sampling means, the ionization means, and the mass spectrometric means, wherein

when a maximum ion intensity of a mass spectrum of the standard sample detected by mass spectrometric means in one measurement system of the plurality of measurement systems is smaller than the predetermined threshold, the sample where a maximum ion intensity of a mass spectrum is detected as one smaller than the predetermined threshold at the one measurement system is transmitted to sampling means of another measurement system except the one measurement system.

12. (amended) The DNA analysis system according to claim 9, further comprising:

a plurality of measurement systems, where each of the measurement systems comprises the sampling means, the ionization means, and the mass spectrometric means, wherein

when a maximum ion intensity of a mass spectrum of the standard sample detected by mass spectrometric means in one measurement system of the plurality of measurement systems is smaller than the predetermined threshold, a sample intended to be measured by the one measurement system is sent to sampling means of another measurement system except the one measurement system.